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Case Series

COVID-19 associated rhinomaxillary mucormycosis: a case series and review of literature

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During COVID-19 pandemic, fulminant deep fungal infection started emerging in India, known as Mucormycosis. This type of mucormycosis was termed as COVID-19 associated mucormycosis (CAM). These patients had previous history of COVID-19 infection. Such cases were mainly reported in immunocompromised patients such as patients with poorly controlled diabetes and chronic renal diseases etc. Rhinomaxillary mucormycosis is an aggressive, fulminant, fatal deep fungal infection of head and neck region. Early diagnosis and prompt treatment can reduce the mortality and morbidity associated with the disease; hence we present case series of rhinomaxillary mucormycosis to create awareness amongst dental surgeons.

Keywords: Mucormycosis. Mucorales. COVID-19. Mycoses.

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Introduction

Mucormycosis is a rare, rapidly spreading, fulminant, opportunistic infection that is caused by a group of filamentous molds[1]. The mortality rate in overall cases of mucormycosis is 54%[2]. This infection is most commonly seen with immunocompromised patients such as human immunodeficiency virus infection, nonhematologic malignancy, diabetes mellitus, and chronic lung disease[3]. Based on anatomic localization, mucormycosis can be classified as one of six forms: 1) rhino-orbital-cerebral mucormycosis (ROCM), 2) pulmonary, 3) cutaneous, 4) gastrointestinal (GI), 5) disseminated, and 6) mucormycosis of uncommon sites[1]. Diagnosis of rhinomaxillary mucormycosis is diagnosed mainly depending upon the clinical features and investigations such as pus/tissue culture and radiology reports[4]. Since mucormycosis is a rare fungal infection, it may cause a diagnostic dilemma for dental clinicians who may not be familiar with clinical presentation even though they may have encountered cases with osteomyelitis of the jaw. As immunocompromised patients are more susceptible to the disease it is important to take a careful case history, meticulous clinical examination, radiologic investigations, hematological investigations can lead to early diagnosis and prompt management with specific fungal therapy, which reduces morbidity and mortality.

Case Report 1

A 58-year-old male patient reported to the Department of Oral Medicine and Radiology with the chief complaint of swelling and pain in the right side of the face for the past 20 days. The patient also gave a history of headache, eye pain, and stuffiness in the nose. Medical history revealed the patient is diabetic for 2 years and he is on insulin injections twice daily. The patient also gave the history of COVID-19 infection 1 month ago and chest HRCT(High resolution computed tomography) with a severity score of 14/40. On clinical examination: periorbital swelling on the right side of the face. [Figure-1] On palpation swelling was soft, tender and a local rise in temperature was felt. On intra-oral examination denuded area of bone was observed extending from 14-18 region. [Figure-2] White coated tongue was noted, which was non-scrapable.

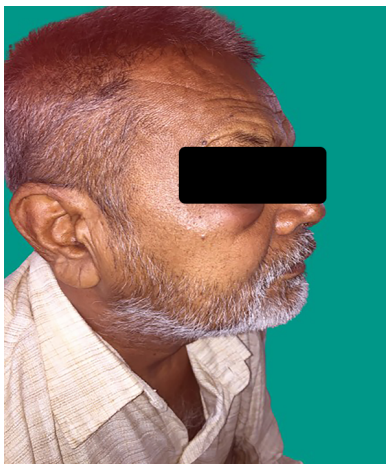

Figure 1. Periorbital swelling on right side.

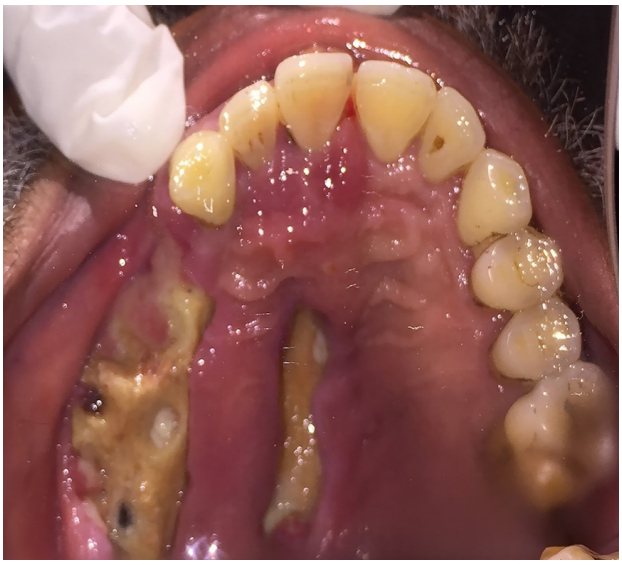

Figure 2. Exposed bone is seen involving right side of maxilla.

Depending upon the clinical findings the provisional diagnosis was given as non-suppurative chronic osteomyelitis and the differential diagnosis was given as mucormycosis.

Further investigations advised were KOH (potassium hydroxide) staining, Computed tomography of paranasal sinus (PNS CT), complete blood count (CBC), random blood sugar (RBS), and glycated haemoglobin test (HbA1c). A swab was taken from the tongue for fungal staining.

Hematologic reports revealed elevated erythrocyte sedimentation rate (ESR) and elevated blood sugar levels.

Axial section of paranasal sinuses (PNS) CT scan revealed hetero-dense soft tissue mass in the right maxillary sinus with thickening of the right nasal mucosa with osteolytic changes in the floor of the maxillary sinus. [Figure -3] The coronal section of CT revealed an ill-defined asymmetric hyperdense mass causing perforation of the medial wall of the sinus [Figure-4]. KOH staining was positive for fungal hyphae. Swab taken from tongue was positive for fungal hyphae. The patient was prescribed clotrimazole 1% w/v mouth paint for topical application 3-4 times daily.

Depending upon the clinical, radiological, and histopathological findings a final diagnosis of rhinomaxillary mucormycosis was made. The patient underwent surgical debridement for necrotic tissue with glycaemic control. Liposomal Amphotericin B 5mg/kg/day was administered for 3 weeks followed by 200 mg t.i.d for 3 weeks.

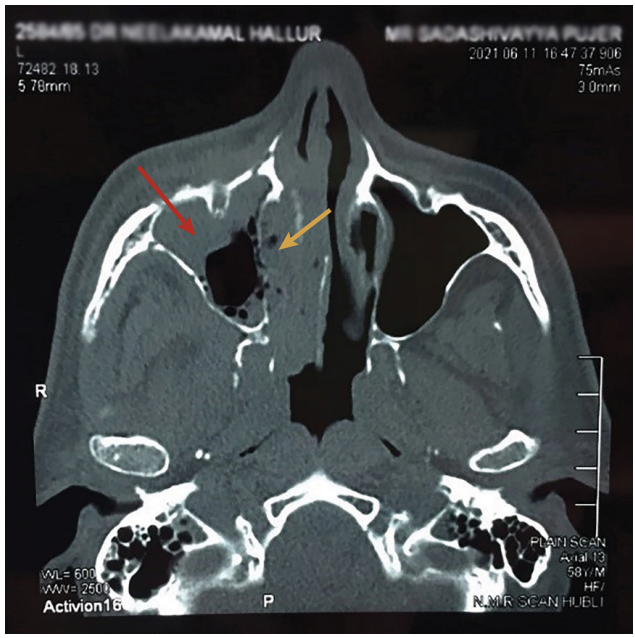

Figure 3. Axial section of CT showing hyperdense mass filling the right maxillary antrum (red arrow) with perforation of nasal cavity with erosion of medial wall of antrum (orange arrow).

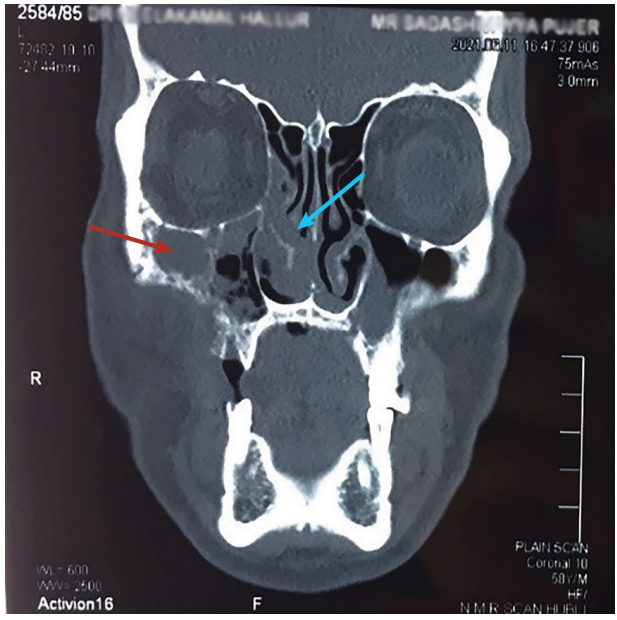

Figure 4. Coronal CT showing a hetero-dense soft tissue mass in the right maxillary antrum (red arrow) perforating and infiltrating into the nasal cavity (blue arrow).

Case Report 2

A 70-year-old, male patient reported to the department of oral medicine and radiology with the chief complaint of swelling on the left side of the face for 10 days.

Medical history revealed the patient is diabetic for 2 years and was currently on insulin for 8 days due to uncontrolled diabetes. The patient also gave a history of fever and malaise 7 days ago. Extra-oral examination revealed lacrimation and proptosis of the left eye [Figure -5]. Multiple coalesced vesicles were noted on the left perioral region and left side of the lower lip with crusting [Figure 6]. Necrosed denuded area of bone with pus discharge was present on the left side of the maxilla i.r.t 26,27 region [Figure-7].

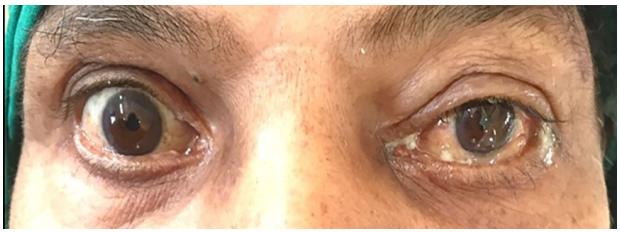

Figure 5. Lacrimation and proptosis of left eye

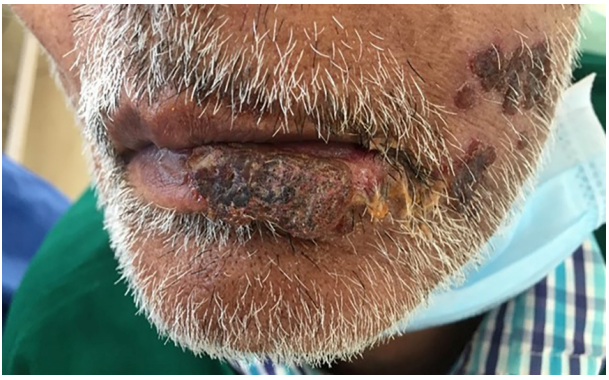

Figure 6. Extra-oral vesicles on the left side of the face with crusting of lips seen.

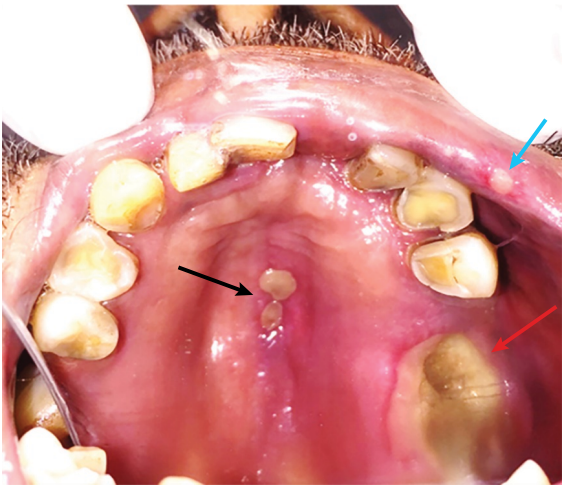

Figure 7. denuded area of bone i.r.t 26,27 (Red arrow), ulcer seen on the midline of hard palate (Black arrow), aphthous ulcer on upper lip (Blue arrow).

Putrid halitosis was noted. Pus discharge from the nose was evident. Coated and swollen tongue was present.

The extra-oral features were suggestive of Herpes zoster infection and for intra-oral lesion provisional diagnosis was considered suppurative osteomyelitis and differential diagnosis of rhinomaxillary mucormycosis was given. Since the patient gave a history of fever 7 days ago RT-PCR was advised to investigate COVID-19. The patient's RT-PCR report was positive, so the patient was sent for treatment of COVID-19. The patient recovered from COVID-19 and reported to the department for a follow-up visit. All the extra-oral vesicles were healed but the intra-oral lesion progressed extensively. [Figure-8]. Intraoral pus swab was sent for culture and sensitivity reports. Further investigations of KOH staining of bone, a biopsy of soft tissue, bone, and computed tomography of paranasal sinus (PNS CT) were advised. Potassium hydroxide staining (KOH Staining) was positive for fungal hyphae. Culture of pus demonstrated growth of Proteus Mirabilis. Intra-oral periapical radiograph (IOPAR) revealed bone with enlarged marrow spaces. Axial section of computed tomography of paranasal sinuses (PNS CT) shows proptosis of the left eye [Figure-9], osteolytic lesion involving left maxilla with perforation of the hard palate in the midline [Figure-10], the left zygoma and sphenoid bone was noted [Figure-11].

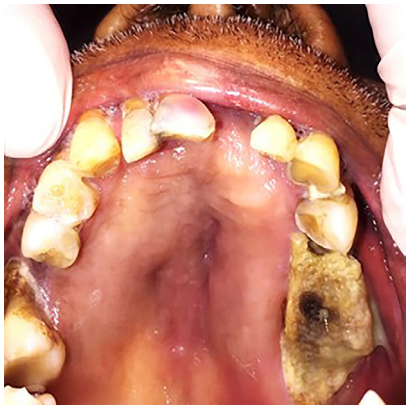

Figure 8. Progression of intra-oral lesion anteriorly pus discharge in the vestibule can be seen.

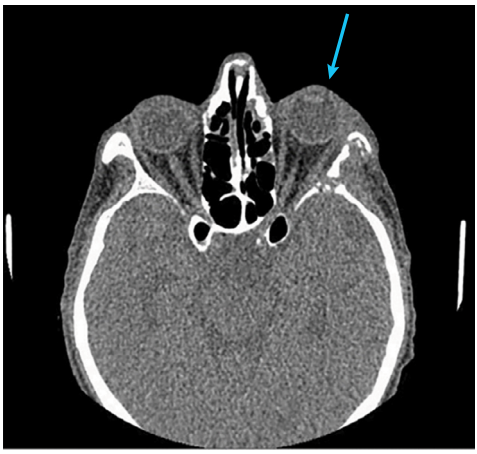

Figure 9. Axial section of CT scan showing proptosis of left eye

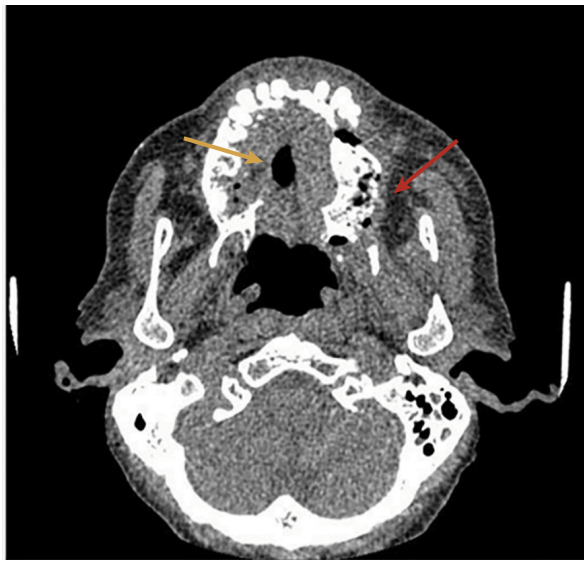

Figure 10. Axial CT showing osteolytic lesion of left maxilla (orange arrow) and perforation of hard palate (red arrow)

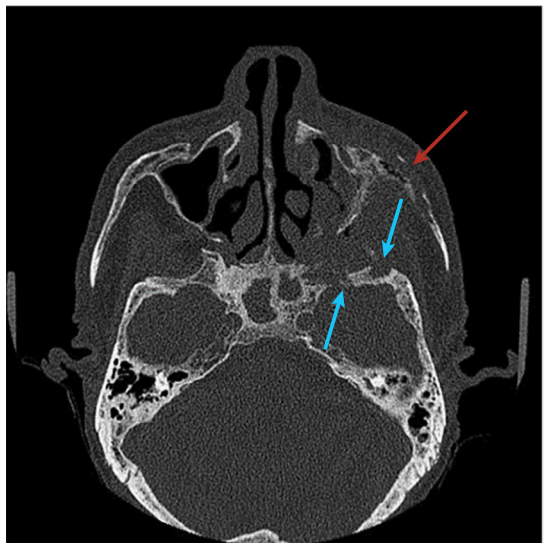

Figure 11. Osteolytic changes involving left zygoma (red arrow), left sphenoid bone seen (blue arrows).

The histopathological report revealed features of osteomyelitis with few bacterial colonies and PAS-positive fungal hyphae. The features were suggestive of a combination of fungal & bacterial osteomyelitis. So, the final diagnosis was a combination of bacterial osteomyelitis with Rhinomaxillary mucormycosis. Micro-debridement through functional endoscopic sinus surgery was done along with liposomal Amphotericin B(5mg/kg/day) injection intravenously with glycaemic control. The patient was planned for surgical debridement and admitted for the same, unfortunately, the patient suffered cardiac arrest and passed away.

Case Report 3

50 years old male patient reported to the department of oral medicine and radiology with the chief complaint of mobile teeth in the upper jaw. Medical history revealed the patient suffered from a COVID-19 infection 1 month ago.

On intra-oral examination multiple intra-oral sinuses with pus discharge were noted in Maxillary anterior and premolar region i.r.t 21,22,24,25[Figure 12]. Grade I mobility noted with 21,22. Depending upon past medical history and clinical features provisional diagnosis of mucormycosis was given. Investigations advised were potassium hydroxide (KOH) staining of pus, contrast magnetic resonance imaging of paranasal sinus (PNS MRI), and haematological investigations such as CBC and RBS were advised. MRI revealed [Figure 13 and 14] marked mucosal thickening of the left maxillary sinus with left periorbital oedema suggestive of invasive fungal sinusitis. KOH staining was positive for fungal hyphae and a final diagnosis of rhinomaxillary mucormycosis was made.

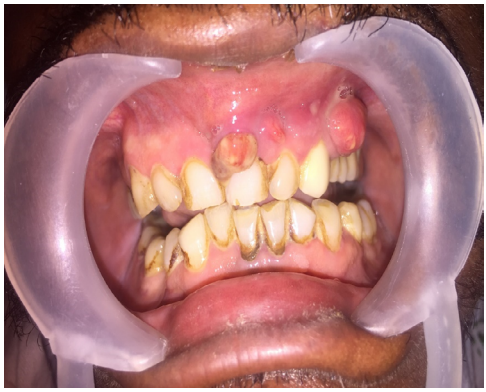

Figure 12. Multiple intra-oral draining sinuses.

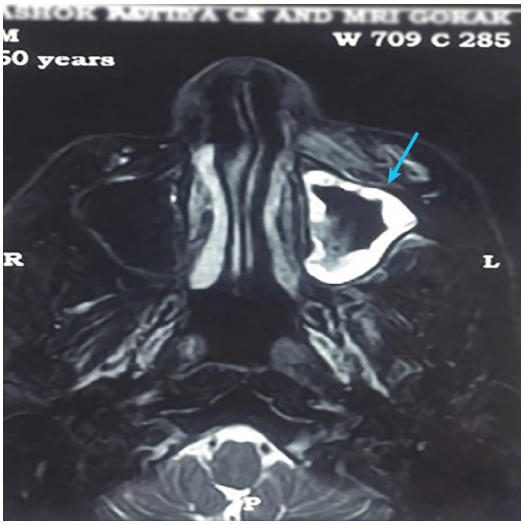

Figure 13. Axial section of PNS MRI showing mucosal thickening of Left maxillary sinus (Blue arrow).

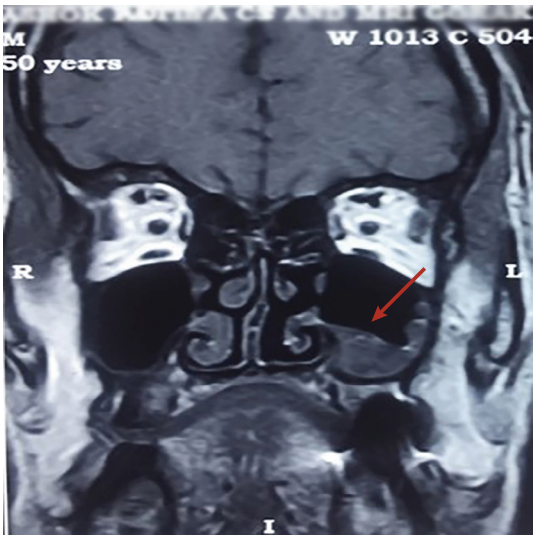

Figure 14. Coronal section of PNS MRI showing mucosal thickening of left maxillary sinus (red arrow) indicative of left maxillary sinusitis.

Micro-debridement was done through functional endoscopic sinus surgery (FESS). The patient was treated with Liposomal Amphotericin B 5mg/kg/day injection intravenously followed by Tab Posaconazole 100 mg 2 tablets twice a day for 20 days.

Discussion

Mucormycosis was first described in 1876 by Furbringer in humans[1]. Mucormycosis is a sudden, rapidly spreading fatal fungal infection caused by a fungus of the class of Zygomycetes and the order of Mucorales. The species most frequently isolated from patients are Apophysomyces (A. variabilis), Cunninghamella (C. bertholletiae), Lichtheimia [Absidia] (L. corymbifera L. raosa), Mucor (M. circinelloides), Rhizopus (R. arrhizus (oryzae) R. microsporus), Rhizomucor (R. pusillus), and Saksenaea (S. vasiformis). These are common environmental organisms that are not harmful to immunocompetent humans[2]. The fungi under Mucorales are ubiquitous, and morphologically appear as broad, aseptate, or sparsely septate ribbon-like hyphae[3]. There are six clinical types of mucormycosis i.e pulmonary, rhinomaxillary (Rhinocerebral), gastrointestinal, cutaneous, disseminated, and mucormycosis of unusual sites[4]. Mucormycosis is most commonly seen in immunocompromised individuals with diabetes, neutropenia and other haematological disorders[3]. The most common clinical type is Rhinomaxillary (Rhino-cerebral) mucormycosis[5]. Recently COVID-related mucormycosis was reported in the literature. During the second wave of COVID-19 India reported most of the cases of mucormycosis, In India, the prevalence of mucormycosis is estimated as 140 per million population, which is about 80 times higher than the prevalence in developed countries[6]. Clinical and experimental data validate those individuals who lack phagocytes or have impaired phagocytic function are at higher risk of mucormycosis. For example, severely neutropenic patients are at increased risk for developing mucormycosis. Surprisingly individuals with HIV are less likely

to develop mucormycosis[7]. In the presence of hyperglycaemia and low pH, which is found in patients with diabetic ketoacidosis (DKA), phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing by both oxidative and nonoxidative mechanisms[8]. Patients on Corticosteroids or immunosuppressed individuals or patients with diabetic ketoacidosis (DKA) has high mortality rate due to progressive pulmonary and hematogenously disseminated infection[9,10].

The skin barrier signifies a host defense against cutaneous mucormycosis, as demonstrated by the increased risk for developing mucormycosis in individuals with interruption of this barrier. The agents of mucormycosis are characteristically incompetent of penetrating intact skin. However, burns, traumatic disruption of the skin, and persistent maceration of skin enables the organism to penetrate deeper tissues. These organisms could originate from traumatic implantation of contaminated soil or water (e.g., the outbreaks after natural disasters, as was seen after the tsunami in Indonesia in 2004 and after the destructive tornadoes that occurred in Joplin, Missouri, in June 2011). Contaminated surgical dressings and nonsterile adhesive tape are the sources of primary cutaneous mucormycosis[11,12]. Patients with rhino-cerebral mucormycosis usually present as acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache, and facial pain. All sinuses can become involved and spread to adjacent structures such as the palate, orbit and brain usually progress rapidly. The hallmarks of the spread of disease beyond the sinuses are tissue necrosis of the palate resulting in palatal eschars, destruction of turbinates, perinasal swelling, and cyanosis of the facial skin overlying the involved sinuses. Black necrotic intranasal or palatal eschar is highly suggestive of the disease but it occurs in only 40–50 % of those affected[13]. Symptoms of Pulmonary mucormycosis are fever, cough, chest pain, dyspnoea and haemoptysis[14]. Some medications used to treat severe COVID-19, including high-dose corticosteroids and tocilizumab, might predispose patients with COVID-19 to mucormycosis. Mucormycosis has been reported in patients with severe COVID-19 infection who lacked other classical mucormycosis risk factors, such as diabetes, conditions or medications that weaken the immune system, and cancer[15,16].

Patients hospitalized for COVID-19 are at risk for nosocomial infections due to long duration of hospitalization and reduced immunity to fight infections[17-20]. Fungal infections resistant to antifungal treatment have also been described in patients with severe COVID-19[21]. Early diagnosis and monitoring for mucormycosis in COVID-19 patients can reduce the morbidity. Healthcare providers should consider medical history, symptoms, physical examinations, and laboratory tests when diagnosing mucormycosis. Biopsy, fungal culture and diagnostic imaging such as a CT scan of head and neck region sinuses plays a vital role in early diagnosis of Rhinomaxillary mucormycosis[22].

Antifungal antibiotics such as amphotericin B, posaconazole, or isavuconazole are most commonly employed in the management of mucormycosis. Amphotericin B, posaconazole, isavuconazole are given intravenously although posaconazole, isavuconazole can also be given by parenteral route[23]. Surgical debridement is the key to controlling and eliminating mucormycosis, but anti-fungal treatment is also typically used in combination. Studies confirm amphotericin-B liposomal 3.0 mg/kg accom-

panied by aggressive surgical debridement, up to and including amputation, is reasonably effective[23,24].

Rhinomaxillary mucormycosis is a fatal, life-threatening opportunistic infection in COVID -19 patients having comorbidities. Most of the patients reported with necrotic bone and multiple intra-oral draining sinus with pus discharge. Tooth mobility was most common complaint in these patients. Early signs and symptoms can play a pivotal role in diagnosis in these patients so that prompt treatment can be provided. Dental clinicians should have adequate knowledge about the disease to provide early diagnosis.

Conflict of interest

Authors declare no conflict of interest.

Informed consent

Informed consent was taken from patients prior to publication.

Author contribution

Sulem Ansari: Case history, clinical examination, Writing and revision of the manuscript. **Jayraj Malik:** Case history, clinical examination of patient. **Anabelle Fernandes:** Case history, clinical examination of patient. **Vaishali Keluskar:** Contributed in the editing of manuscript. **Shivayogi Charantimath:** Contributed in writing and editing of the manuscript and provided clinical diagnosis.

References

1. Fürbringer P. [Observations on pulmonary mycosis in humansn]. Virchows Arch Path Anat. 1876;66:330-5. German. doi: 10.1007/BF01878266.
2. Hernández JL, Buckley CJ. Mucormycosis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
3. Prakash H, Chakrabarti A. Global Epidemiology of Mucormycosis. J Fungi (Basel). 2019 Mar;5(1):26. doi: 10.3390/jof5010026.
4. Centers for Disease Control and Prevention. Information for Healthcare Professionals about Mucormycosis. 2020 May 27 [cited 2021 Jun 19]. Available from: https://www.cdc.gov/fungal/diseases/mucormycosis/health-professionals.html.
5. Chakrabarti A, Singh R. Mucormycosis in India: unique features. Mycoses. 2014 Dec;57 Suppl 3:85-90. doi: 10.1111/myc.12243.
6. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021 Jul-Aug;15(4):102146. doi: 10.1016/j.dsx.2021.05.019.
7. Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 6.ed. Philadelphia: Elsevier-Churchill Livingstone; 2005.
8. Chinn RYW, Diamond RD. Generation of chemotactic factors by Rhizopus oryzae in the presence and absence of serum: Relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis. Infect Immun. 1982 Dec;38(3):1123-9. doi: 10.1128/iai.38.3.1123-1129.1982.

9. Chamilos G, Lewis RE, Lamaris G, Walsh TJ, Kontoyiannis DP. Zygomycetes hyphae trigger an early, robust proinflammatory response in human polymorphonuclear neutrophils through toll-like receptor 2 induction but display relative resistance to oxidative damage. Antimicrob Agents Chemother. 2008 Feb;52(2):722-4. doi: 10.1128/AAC.01136-07.

10. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against Rhizopus. J Clin Invest. 1984 Jul;74(1):150-60. doi: 10.1172/JCI111395.

11. Gartenberg G, Bottone EJ, Keusch GT, Weitzman I. Hospital-acquired Mucormycosis (Rhizopus rhizopodiformis) of skin and subcutaneous tissue . N Engl J Med. 1978 Nov 16;299(20):1115-8.

12. Mead JH, Lupton GP, Dillavou CL, Odom RB. Cutaneous Rhizopus infection. Occurrence as a postoperative complication associated with an elasticized adhesive dressing. JAMA. 1979 Jul;242(3):272-4. doi: 10.1001/jama.242.3.272.

13. Rajagopalan S. Serious infections in elderly patients with diabetes mellitus. 2005 Apr;40(7):990-6. doi: 10.1086/427690.

14. Lin E, Moua T, Limper AH. Pulmonary mucormycosis: clinical features and outcomes. Infection. 2017 Aug;45(4):443-8. doi: 10.1007/s15010-017-0991-6.

15. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. Mycopathologia. 2021 May;186(2):289-98. doi: 10.1007/s11046-021-00528-2.

16. Kanwar A, Jordan A, Olewiler S, Wehberg K, Cortes M, Jackson BR. A fatal case of rhizopus azygosporus pneumonia following covid-19. J Fungi (Basel). 2021 Feb;7(3):174. doi: 10.3390/jof7030174.

17. Nucci M, Barreiros G, Guimarães LF, Deriquehem VAS, Castiñeiras AC, Nouér SA. Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. Mycoses. 2021 Feb;64(2):152-6. doi: 10.1111/myc.13225.

18. Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clin Microbiol Infect. 2020 Oct;26(10):1395-9. doi: 10.1016/j.cmi.2020.06.025.

19. Posteraro B, Torelli R, Vella A, Leone PM, De Angelis G, De Carolis E, et al. Pan-echinocandin-resistant candida glabrata bloodstream infection complicating covid-19: A fatal case report. J Fungi (Basel). 2020 Sep;6(3):163. doi: 10.3390/jof6030163.

20. Meijer EFJ, Dofferhoand ASM, Meis JF, Hoiting O, Buil JB. Azole-resistant COVID-19-associated pulmonary aspergillosis in an immunocompetent host: a case report. J Fungi (Basel). 2020 Jun;6(2):79. doi: 10.3390/jof6020079.

21. Centers for Disease Control and Prevention. Fungal diseases. Diagnosis and testing of Mucormycosis. 2021 Jan 14 [cited 2021 Jun 20]. Available from: https://www.cdc.gov/fungal/diseases/mucormycosis/diagnosis.html.

22. Centers for Disease Control and Prevention. Fungal diseases. Treatment for Mucormycosis. 2021 Jan 14 [cited 2021 Jun 20]. Available from: https://www.cdc.gov/fungal/diseases/mucormycosis/treatment.html.

23. Losee JE, Selber J, Vega S, Hall C, Scott G, Serletti JM. Primary cutaneous mucormycosis: Guide to surgical management. Ann Plast Surg. 2002 Oct;49(4):385-90. doi: 10.1097/00000637-200210000-00009.

24. Sun H-Y, Singh N, Singh N, Sun H-Y. Mucormycosis: its contemporary face and management strategies. Lancet Infect Dis. 2011 Apr;11(4):301-11. doi: 10.1016/S1473-3099(10)70316-9.